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BRIEF COMMUNICATION

Right Sited Renal Cell Carcinoma Metastasizing to the Contralateral Ovary: Case Report and Review of the Literature

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Abstract Ovarian metastases from renal cell carcinoma are rare, with only 22 cases reported in the literature. We report a case of a 45-year-old woman, who developed left ovarian and right adrenal metastases 3 months after diagnosis of clear cell renal cell carcinoma and review the literature. This is the fourth reported case of right renal cell carcinoma metastasizing to the left ovary. The patient is alive 4 years after resection of the ovarian tumor, treated with sunitinib. We conclude that, although rare, metastatic renal cell carcinoma should be included in the differential diagnosis of ovarian tumors with clear cell histology.

Keywords Renal cell carcinoma · Ovarian metastasis

Introduction

Renal cell carcinoma (RCC) represents 3% of adult tumors and it usually appears in 50 to 70 year-old individuals [1]. In most cases renal tumors grow symptom less in the retroperitoneal area and metastases already exist in 30% of patients at the time of diagnosis. RCC most frequently metastasizes to lung, bones, adrenals, liver and skin, but is well known for its propensity to metastasize to unusual sites via haematogenous spread [1]. Ovarian metastases from RCC are rare, but can be mistaken with primary clear cell ovarian carcinoma, due to their histological similarity. The differential diagnosis is difficult, especially when the ovarian metastasis is discovered prior to the renal primary. We report a case of right sited RCC with contralateral ovarian and homolateral adrenal metastases and review the literature.

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Case Presentation and Management

A 45-year old woman was referred to the Oncology Unit of Sotiria General Hospital for scheduled post-operative imaging. Three months ago, she had undergone radical right nephrectomy for renal cell carcinoma of clear cell type. There was no direct capsular invasion. Renal vein invasion had been detected on computed tomography (CT) scans at that time.

The patient was symptom-free. At re-staging, abdomen CTs revealed a mass of mixed texture in the right suprarenal area and a cystic mass in the lower pelvis, most probably of left appendage origin (Fig. 1a). Magnetic resonance imaging (MRI) of the upper and lower abdomen confirmed the CT scan findings (Fig. 1b). No lymphadenopathy, or evidence for intraperitoneal, pulmonary or other metastatic disease was detected. No secondaries were identified on bone scintigraphy.

Serum levels of carcinoembryonic antigen (CEA), CA-125, CA19–9 and alpha feto-protein were within normal limits. A fine needle aspiration biopsy was taken from the suprarenal mass and the histological findings were indicative of metastatic renal cell carcinoma. The patient

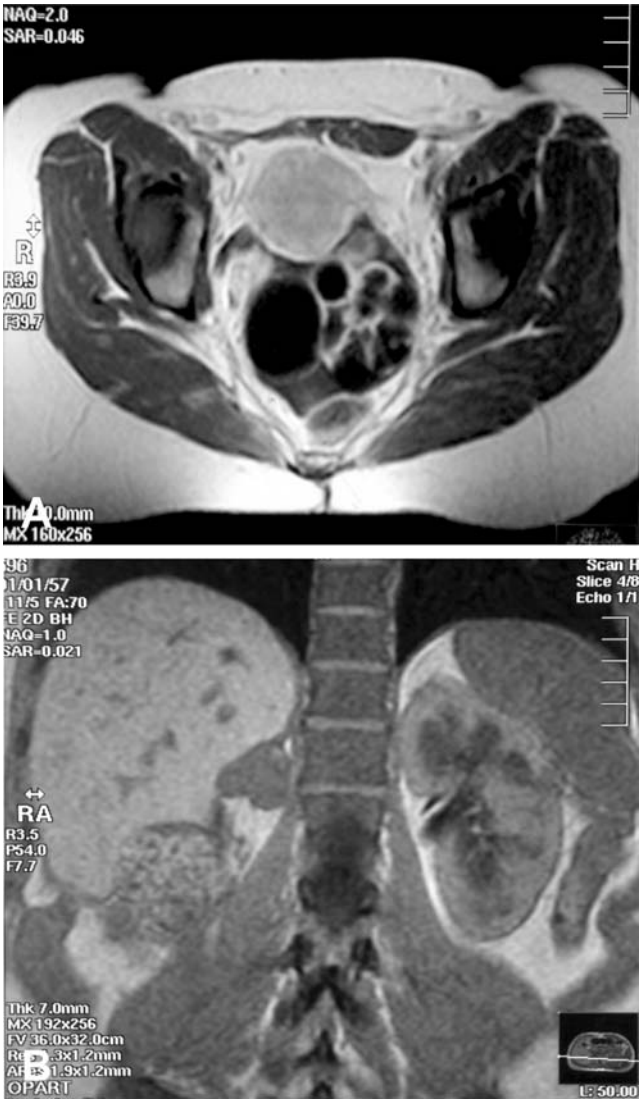

Fig. 1 **a** Abdomen computed tomography scan: Cystic formation (8 cm in diameter) in the lower pelvis, between the uterus and the rectum. **b** Abdomen magnetic resonance imaging: Mass of non-homogeneous texture (3×2.5×3 cm) in the area of the right suprarenal gland

underwent right adrenalectomy and left oophorectomy. Patient's informed consent was obtained prior to any diagnostic tissue evaluation. The case was retrieved from the archive of the Pathology Department of Sismanoglion Hospital with the approval of the Sismanoglion Ethics Committee and in accordance with the ethics standards described by the Helsinki Declaration of the World Medical Association (2000).

Pathologic findings The left ovary and right adrenal were replaced by a 10×7.5×5.5 cm hemorrhagic cystic mass and a 1.8 cm in greatest diameter white-tan mass respectively. Histology showed dilated neoplastic glandular structures embedded in loose fibrous stroma (Fig. 2). The neoplastic glands were lined by medium-sized cells with hyperchromatic, pleomorphic nuclei and eosinophilic or clear cytoplasm. Their lumen contained erythrocytes. Few mitotic figures were evident. Immunohistochemically, the neoplastic cells were positive for low molecular weight cytokeratins, vimentin and epithelial membrane antigen (EMA), while they were negative for chromogranin, synaptophysin and CEA (Fig. 2). Negative control sections, in which the primary antibody was omitted, were used in every immunostaining run. Transverse section of colonic wall and breast carcinoma were used as positive controls for cytokeratins and EMA and vimentin respectively. The histological and immunohistochemical findings were consistent with metastatic renal cell carcinoma.

Postoperatively, the patient received interferon and she developed progressive disease 9 months later. Subsequently she was treated with sunitinib and her disease stabilized. She is alive with widespread metastases 4 years after diagnosis of the renal primary, and stable disease on sunitinib.

Discussion

Ovaries are a common site for distant metastases from non genital tumors, especially stomach, colon and breast carcinomas [2]. Approximately 7% of ovarian tumors presenting clinically as ovarian primaries are identified as secondaries on histological examination [2]. RCC metastasizes rarely to the ovaries, with only 22 cases reported in the literature from 1937 onwards. This may be attributed to ovarian atrophy and decreased blood perfusion due to vascular sclerosis in most postmenopausal women who are at the age of peak incidence of RCC. The 22 relevant cases [3–13] are analyzed including the present case and summarized in Table 1.

The age group ranged from 17 to 68 years. The left kidney was the site of primary in 11 cases (48%), in two cases the primary laterality was not listed, in one case bilateral renal RCC was diagnosed [7] and in the remaining nine cases—including the present case—(39%) the right kidney was the site of the primary tumor.

Left ovarian metastases were detected in ten cases (43%), the right ovary was involved in four cases (17%), ovarian laterality was not listed in one case and bilateral ovarian tumors were detected in eight cases (35%). Four of the right sited RCCs metastasized to the contralateral ovary (44.4%), two to the ipsilateral ovary (22.2%) and two gave bilateral ovarian metastases (22.2%). Five of the left sited RCCs metastasized to the left ovary (45.4%), two to the

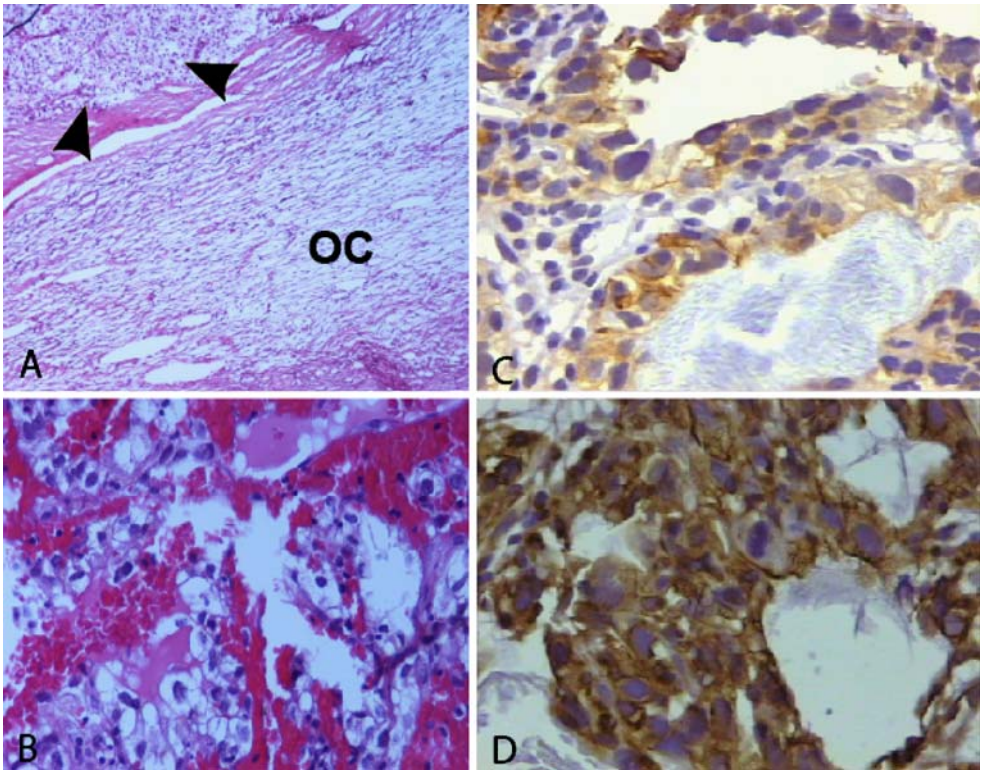

Fig. 2 **a** Metastatic renal cell carcinoma (*arrowheads*), ovarian cortex (*OC*), H & E, ×100. **b** Higher magnification of RCC depicted in **a**, blood-filled glandular structures lined by neoplastic cells with clear cytoplasm and nuclear hyperchromasia, H & E, ×400. Tumor cells showing immunohistochemical positivity for low molecular weight cytokeratins (**c**) and vimentin (**d**). Streptavidin-biotin immunohistochemical method, 3′,3′-diaminobenzidine (chromagen), Hematoxylin counterstain, ×400

right ovary (18%) and in four cases (36.3%) bilateral ovarian metastases were detected.

The data above are suggestive of a slightly higher tendency of left-sided RCC to metastasize to the ovaries: retrograde venous tumor spread seems to be facilitated by the direct drainage of the left ovarian into the left renal vein. We report the fourth case of right-sided RCC metastasizing to the left ovary, suggesting that there may be routes for metastatic spread of RCC, other than tumor embolization through the left ovarian vein to the uterovaginal venous plexi.

In 15 cases (65.2%), the diagnosis of RCC preceded the detection of ovarian metastases with a time interval ranging from 3 months to 14 years. Renal and ovarian tumors were mainly detected within the first 4 years after RCC diagnosis. In the present case, left ovarian and right adrenal metastases were detected 3 months after RCC diagnosis. In 4 cases (17%), the ovarian tumors were detected before the diagnosis of RCC. Young et al reported an interesting case of renal primary detected 8 years after ovarian tumor diagnosis [13]. In three cases the ovarian tumor was treated as primary ovarian adenocarcinoma until the appearance of other metastases prompted the discovery of its true origin [9, 13]. Synchronous ovarian metastases were identified in three cases (13%). Surgery was the main treatment, with radiation, chemotherapy and interferon used in several cases. Information on long term survival was limited. However, in well documented cases overall survival ranged from 3 months to 16 years [3–5, 7–13].

Metastatic RCC should be distinguished from primary ovarian clear cell carcinoma and other clear cell tumors of the ovary, such as steroid cell tumor and dysgerminoma [2]. The differential diagnosis between primary ovarian carcinoma and metastatic RCC can be difficult, especially when the latter is diagnosed first. Presence of hobnail and flattened cells, intra-luminal mucin and hyaline membranous material are indicative of an ovarian origin, while a sinusoidal vascular pattern is more prominent in RCC [2]. In our case, histology revealed glandular structures containing erythrocytes and was consistent with a renal cell carcinoma origin.

Immunohistochemistry has become an important tool in the differential diagnosis of clear cell adenocarcinomas of the ovary [14]. Ca-125 is commonly expressed in ovarian adenocarcinomas but is typically absent in renal cell carcinomas. The RCC is expressed in 80–90% of renal tumors and CD10 (common acute lymphoblastic leukaemia antigen) has been successfully used to distinguish RCC from other clear cell tumors. Nolan et al. proposed an immunohistochemical panel to aid the differential diagnosis between primary ovarian clear cell carcinoma and meta-

Table 1 Summary of the reported cases of clear cell renal cell carcinoma metastasizing to the ovaries

No	Age	Laterality	Renal ovarian	Detection of ovarian metastasis	Treatment	Outcome	Reference
1	39	Left	Left	21 months later	Surgery/radiation	3 months, dead	Stadiem et al, 1937
2	66	Right	Right	6 months later	Not listed	2 years, alive df	Martzloff et al. 1937[a]
3	64	Right	Bilateral	11 years later	Not listed	147 months, dead	Bruegge et al. 1957[a]
4	33	Not listed	Bilateral	6 years later	Surgery/radiation	19 months, alive	Johansson et al. 1960
5	68	Right	Left	3 months later	Surgery	2 years, alive	Stefani et al. 1983
6	52	Left	Left	Detected first	Not listed	11 days, alive	Buller et al. 1983[a]
7	28	Not listed	Bilateral	Not listed	Not listed	Not listed	Liu et al. 1992
8	48	Right	Left	Detected first	Not listed	8 years, alive	Young et al. 1992
9	62	Left	Right	1 year later	Not listed	6 months, alive	Young et al. 1992
10	48	Left	Left	Detected first	Not listed	Not listed	Young et al. 1992
11	40	Left	Bilateral	7 months before	Surgery/radiation	55 months, alive, wd	Spencer et al. 1993
12	54	Right	Left	3 years later	Surgery	3 years, alive	Fields et al. 1993[a]
13	46	Left	Bilateral	3 years later	Surgery	6 years, alive, df	Adachi et al. 1994[a]
14	66	Right	Bilateral	14 years later	Surgery	16 years, alive, df	Vara et al. 1998[a]
15	47	Left	Left	4 years later	Surgery	4 years, alive	Shinojima et al. 2001
16	48	Left	Bilateral	Synchronous	Surgery/3cy CMT	3 months, alive	Hammock et al. 2003[a]
17	50	Right	Right	12 months later	Surgery	6 months, lost to follow up	Insabato et al. 2003
18	49	Right	Not listed	14 months later	Surgery	20 months, dead	Insabato et al. 2003
19	17	Left	Left	2 years later	Surgery	24 months, alive, df	Insabato et al. 2003
20	61	Left	Bilateral	7 years later	Surgery/ interferon	9 years, alive	Valappil et al. 2004
21	52	Left	Right	Synchronous	Surgery	10 months, dead	Kato et al. 2006
22	42	Bilateral	Left	Synchronous	Surgery/ interferon	2 years, alive, df	Madersbacher et al. 2007
23	45	Right	Left	3 months later	Surgery/ interferon	4 years, alive, wd	Present case

df Disease free, *wd* widespread disease, *surgery* radical nephrectomy and bilateral salpigo-oophorectomy or ovarian mass excision
[a] Reviewed in Valappil et al 2004

static RCC consisting of CA-125, estrogen receptor, progesterone receptor, the anti-cytokeratin antibody 34βE12 and vimentin [15].

Vimentin is an intermediate filament protein typically present in cells of mesenchymal origin and is commonly identified in renal cell carcinomas [15]. The majority of clear cell RCCs shows a restricted expression of low molecular weight cytokeratins and vimentin [16]. High molecular weight cytokeratin (HMWCK) and cytokeratin 7 (CK7) are rarely expressed in clear cell RCCs [16], whereas clear cell ovarian carcinomas are almost always positive for CK7 [14]. The typical immunohistochemical profile of our case (vimentin+, low molecular weight cytokeratins+, EMA+) supported further the diagnosis of a metastatic RCC.

In summary, ovarian metastasis appears early in the metastatic pathway of RCC. The possibility of disease progression involving the ovaries should be considered in women with a history of RCC. Moreover, metastatic renal cell carcinoma should be included in the differential diagnosis ovarian clear cell carcinoma. Careful gross and histological examination combined with application of a panel of immunohistochemical markers may distinguish a metastatic renal from a primary ovarian clear cell carcinoma. Early diagnosis of this rare metastatic tumor results in prompt treatment and prolonged patient survival.

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